Generic and Brand-Name AEDs Bioequivalent

BY JEFF EVANS

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

TORONTO — Most generic formulations of antiepileptic drugs have pharmacokinetics that closely match their brand-name reference, according to an analysis of bioequivalence studies submitted to the Food and Drug Administration.

These results suggest that most switches from brand-name to generic formulations of antiepileptic drugs (AEDs) are safe and do not lead to clinically significant changes in blood concentrations, Dr. Gregory L. Krauss said.

However, he cautioned that generic-to-generic switches of AED formulations should be minimized because simulations of these switches in his study resulted in a wide variability of blood concentrations, particularly for AEDs with low solubility.

"This is an unaddressed area in U.S. regulations, but there are over 500 potential switches between different pairs of generic AEDs at the same dose," said Dr. Krauss, professor of neurology at Johns Hopkins University, Baltimore. "Switches between generic formulations may cause undesirable shifts in AED concentrations. These sorts of patterns should be examined in clinical studies, particularly ones that would enroll patients who are intolerant to AEDs, elderly, or taking polytherapy."

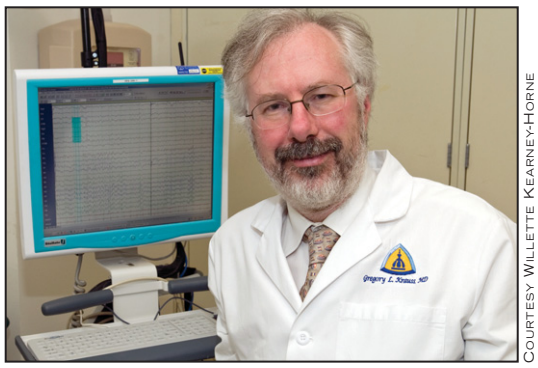
After several years of sending Freedom of Information Act data requests to the FDA, Dr. Krauss and his associates at Johns Hopkins were eventually able to collaborate on the study with officials at the agency.

Bioequivalence is determined in randomized, crossover, pharmacokinetics studies with a small number of healthy volunteers who receive single doses of the generic and references drugs.

In these studies, the FDA defines a test product to be bioequivalent to a reference product when the 90% confidence intervals for test-to-reference ratios of the area under the plasma concentration time curve (AUC) and the maximum plasma concentration (C_{max}) are within an acceptance range of 80%-125%. AUC measures how much drug is absorbed in a given time, whereas C_{max} measures the maximum plasma concentration of a drug.

The investigators examined 147 AED formulations, excluding extended-release products, in 251 bioequivalence studies. All 7,125 participants in these studies were adults (mean age, 32 years; 79% male), but only 44 were older than 65 years.

Overall, 54% of the participants were white, 26% were Asian, 10% were black, 3% were Hispanic, and 7% were other race/ethnicity.



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In terms of intersubject variability, "there's really no difference," Dr. Gregory L. Krauss said.

In 99% of the studies, the AUC for both reference and generic formulations varied by less than 15%. In comparison, 89% of C_{max} studies found that measurements between reference and generic formulations varied by less than 15%. The remaining bioequivalence studies evaluated formulations with AUC and C_{max} measurements that varied 15%-25%.

For example, divalproex generic products were largely similar to Depakote in terms of AUC and C_{max}. But some products did not perform as well as others and had very broad 90% confidence intervals for both AUC and C_{max}.

Some generic AEDs had confidence intervals for AUC or C_{max} ratios that were much less or much greater than a ratio of 1, meaning that for some switches one would expect slightly lower blood concentrations of the active ingredient and for other switches one would expect slightly higher blood concentrations.

But when a switch is made from a generic formulation of a drug with a confidence interval completely below 1 to a generic formulation with a confidence interval completely above 1, Dr. Krauss noted that there is likely to be a bigger change in blood concentration than with brand-name to generic switches.

The investigators found generally greater differences in C_{max} between generic and reference formulations than they did for AUC. One of the greatest differences in C_{max} was found in carbamazepine formulations. For instance, only 9% of generic formulations of carbamazepine were within 5% of the reference product, whereas 64% of formulations were within 5%-10% of the reference, 18% were within 10%-15%, and 9% were within 15%-25%.

Reference drugs did not provide more stable delivery of active ingredients to individuals, compared with generic formulations. The standard deviations between the generic formulations and a reference drug were nearly identical for most drugs. In terms of intersubject variability, "there's really no difference," Dr. Krauss said. ■

Disclosures: *Dr. Krauss said neither he nor his colleagues had relevant conflicts.*

MY TAKE

Study Did Not Examine the Real At-Risk Population

The data presented by Dr. Krauss give us a deeper understanding of the variability among generic AED products. It is important to note that this study is based on data generated from people who will never take an AED. These normal subjects received only a single dose of the drug and were not taking any concomitant medications. There are large potential differences between this population and patients with epilepsy who are taking two or three other AEDs or non-AEDs and who might be older have taken an AED daily for many years. Those are the people in whom I'm most concerned about therapeutic equivalence.

There may be subsets of individuals who are at increased risk for seizures with small changes in bioequivalence, such as those who have had life-threatening status epilepticus in the past, pregnant women, people with epilepsy who have been seizure free for many years, and people with other serious medical conditions.

We don't really know what percentage change in AUC or C_{max} between products is actually safe—that is, which ranges of bioequivalence translate to therapeutic equivalence and which do not. In his study, Dr. Krauss is suggesting that certain ranges of difference between products should be safe and others perhaps not so safe. Unfortunately, we have no data to support that inference. There are no data providing evidence that 90% confidence intervals in the 80%-125% range, which are the current FDA standard, translate to therapeutic equivalence. The FDA created this range based on expert opinion.

A recent FDA advisory committee indicated that the range for generic AED confidence intervals may not be optimal for patients with epilepsy, but the committee did not agree upon any specific recommendations.

The FDA states that all brand name–to-generic or generic-to-generic switches are safe for all people with epilepsy. I believe the only way to test this is to perform a prospective, randomized study of people with epilepsy.

MICHAEL PRIVITERA, M.D., *is a professor of neurology at the University of Cincinnati and is director of the Cincinnati Epilepsy Center. He has received research funding and honoraria for speaking or consulting from UCB, Johnson & Johnson, Pfizer, Eisai, the National Institutes of Health, and the American Epilepsy Society.*

Antiepileptic Side Effects a Problem for 40% of Patients

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

TORONTO — About 40% of epilepsy patients are bothered by side effects of their antiepileptic drugs, based on data from a survey of adults with epilepsy.

Information on the tolerability of antiepileptic drugs (AEDs) and the reasons for discontinuing treatment are limited, George J. Wan, Ph.D., said in a poster.

To examine drug tolerability and treatment satisfaction, Dr. Wan and his colleagues reviewed data from the National Survey of Epilepsy, Comorbidities, and Health Outcomes (EPIC), a large U.S. survey conducted in 2009 that included 7,500 epilepsy patients and 2,500 controls.

A total of 2,395 respondents reported being formally diagnosed with epilepsy or a seizure disorder; of those, 1,415 (59%) were taking antiepilepsy drugs at the time of the survey. About 60% of the respondents reported taking one AED, 35% reported taking two or three, and 5% reported taking four or more.

A total of 772 respondents said that they were "not at all" bothered by side effects from AEDs. But 519 respondents reported some degree of bother: 22% were mildly bothered; 12%, moderately bothered; 5%, markedly bothered; and 1%, extremely bothered. The researchers did not identify specific side effects.

Overall, 72% of the respondents said they were either "somewhat satisfied" or "very satisfied" with their current AED regimens. But 304 respondents said that they had discontinued their medications. Of those, 50% discontinued on their doctor's advice; 45% because of side effects; 30% because of improvement in seizures; and 21% because of inadequate seizure control. Some respondents indicated more than one reason for discontinuing their AEDs.

Patients taking two or more AEDs were significantly more likely to be bothered by side effects, compared with those taking one, the researchers reported. ■

Disclosures: *Dr. Wan is an employee of Ortho-McNeil Janssen Scientific Affairs, which supported the study.*